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RESEARCH PROJECT INITIATION

Date: April 18, 1972

Project Title: Research Initiation - Electrical Stimulation of the Peripheral Auditory System

Project No: E-21-616

Principal Investigator Dr. H. N. Nunnally

Sponsor: National Science Foundation

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RESEARCH PROJECT TERMINATION

Date: January 8, 1975

Project Title: **Research Initiation - Electrical Stimulation of the
Peripheral Auditory System**

Project No: **E-21-616**

Principal Investigator: **Dr. H. N. Nunnally**

Sponsor: **National Science Foundation**

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E-21-616

GEORGIA INSTITUTE OF TECHNOLOGY

ATLANTA, GEORGIA 30332

SCHOOL OF
ELECTRICAL ENGINEERING

April 11, 1973

National Science Foundation
Electrical Sciences and Analysis
Program
Engineering Division
Washington, D.C. 20550

Ref: Research Initiation Grant No. GK-32653 - "Electrical Stimulation of the
Peripheral Auditory System"

Gentlemen:

I am pleased to submit the following report covering the first nine months of
effort under the subject grant.

Work Accomplished

The work done to date has concentrated on the achieving of the first goal
of the research proposal--the demonstration that elements of the auditory nerve
can be excited by voltages applied very near the basilar membrane. This effort
has involved the design and construction of a prototype stimulating electrode
system and its subsequent testing in experimental animals. This was done after
a visit by the principal investigator to the laboratory of R. P. Michelson,
whose published reports (1, 2, 3) formed the basis of the original proposal.
Also, considerable time has been used for training two graduate research assis-
tants in performing the surgical procedures necessary to expose and instrument
the guinea pig auditory nerve.

The design philosophy for the stimulating electrode system as originally
proposed called for ball-type electrodes to be pushed through the round window
and carefully placed on the basilar membrane. While this technique is possible
(and some effort was devoted to this approach) there are certain drawbacks
which became apparant as work progressed. One problem (as mentioned in the
proposal) is that such a configuration would most likely be limited in effects
to a small fraction of the nerve fiber population because of its restricted size.
Secondly, the approach sacrifices completely the current-directing capability of the
electrode used clinically by Michelson. That is, Michelson's electrode, because
it is mounted on a silastic base which fills most of the scala tympani cross-
section, forces the stimulating current through the basilar membrane and organ
of corti. Finally, examination of several guinea pig preparations revealed that
from a mechanical standpoint the electrode placement would be quite difficult to
visualize under the operating microscope.

Therefore, an alternate electrode and positioning scheme was sought which
would overcome the above objections. Such a system has been formulated, based
on results very recently given by Kohlloffel (4). He showed that a rather large
hole (.5 mm x 2mm) can be made in the bone overlying the scala tympani of the
first turn without seriously affecting the ear's response as measured with cochlear
microphonic recordings. This technique, then, offers a means of access to the

scala tympani thru which a rather large electrode structure can be placed. Thus an electrode was designed which consisted of two 1.2mm lengths of 0.002" diameter gold wire mounted in parallel about 1mm apart on a 0.5mm plastic base. The base was fashioned so that the electrode wires can be inserted through the hole in the scala tympani. This electrode technique promises to give a larger current spread and to be more effective in forcing currents in the desired locations than the originally proposed system.

The electrode has been tested in two guinea pigs which were instrumented for auditory nerve fiber response measurements. Neither animal showed fiber responses which could be attributed to the currents passed by the electrode. Current magnitude was 50-100 μ a (peak-to-peak) and was provided by a specially constructed isolated stimulator circuit. There are two possible explanations for this initial lack of electrical response. In the first place, both of the animals tested showed very high acoustic thresholds (about 60 dB SPL) for fiber response, indicating that some deterioration in the auditory system had occurred. Secondly, because the electrode system still allows some perilymph between the wires and the bottom of the basilar membrane, the current may be bypassing the organ of Corti. An associated problem is that the stimulus artifact through the microelectrode accompanying these currents is quite large. It should be recalled that Michelson (1) claims that 0.02 μ a is sufficient current for stimulation of the nerve fibers. Hence, it is still not known whether the present electrode system will be successful in stimulation. The answer will come after tests in animals whose auditory fibers show reasonably normal acoustic thresholds.

Work Remaining

The work yet to be done must proceed along several fronts.

(1) Surgical techniques of auditory nerve exposure must continue to be improved so that preparations with reasonably normal hearing are available for testing.

(2) The stimulus artifact problem must be solved. It is felt that this can be handled by a combination of differential recording, as used in the recently published work of Moxon (5), and stimulating electrode impedance reduction thru the use of either platinum black or special silver-silver chloride material instead of metallic gold.

(3) Further in vivo testing of the electrode must be done. If the electrode configuration still proves inadequate, alternatives must be sought.

(4) Assuming successful stimulation is achieved, the second research objective--the characterization of the electrically induced responses--should follow readily.

In summary, even though progress in electrode design has been made, and some testing has been accomplished, neither of the stated research goals have been obtained at present. However, our experimental techniques are now fairly well established, and I hope to see substantial steps toward meeting the first objective in the next few months.

H. N. Nunnally, J. H. Schlag, and R. P. Webb

We have conducted two series of experiments to investigate the effects of electrical currents injected into the cochlea as manifested in responses from single primary auditory nerve fibers in the guinea pig. In the first series, direct currents were passed across the cochlear partition, while in the second, audio-frequency currents were driven through a 3-mm segment of the basal turn scala tympani. Results from the first experiments bear upon our understanding of the electrophysiology of audition, and those from the second series have implications for the use of cochlear stimulation as a possible treatment for sensorineural deafness.

In the two sets of experiments, young adult guinea pigs were anesthetized, artificially respired, and placed under an automatic body temperature control system. The cochlea was exposed ventrally, and single unit responses were obtained from microelectrodes inserted into a small hole drilled at the base. Response data were reduced directly to spike event times and recorded on digital tape (for off-line analysis) with a computer system interfaced with the stimulus waveform generator. Audio-frequency stimulation currents were obtained from an isolated source driven with the waveform generator. The dc source was an isolated, relay-controlled battery pack which could supply both long-term currents and short current bursts synchronized to fall within 80-msec acoustical tone bursts.

Long-term dc experiments verify results obtained earlier by Teas et al. (1), namely, that currents passed in the direction vestibuli-tympani (V-T) enhance auditory evoked response, while oppositely directed currents reduce sensitivity. However, we were interested in the response transients associated with current "make" and "break"--information not available from that work. Therefore, we studied the effects of short current pulses (40 msec) applied in the middle of acoustic tone bursts. Results show that the current effect is immediate and that resulting post stimulus time (PST) histograms have an adaptive characteristic during the current interval that is suggestive of the adaptation normally seen in histograms reflecting acoustic stimulation alone. We have interpreted these results in terms of an interaction of two effects--the first being a change in the hair cell resting potential, and the second the well-known modification of the cochlear microphonic under the influence of direct current.

Our basis for performing the audio-frequency series was the growing number

of clinical investigations which have explored the possibilities of giving auditory sensations to patients with profound sensorineural deafness through stimulation of the organ of Corti or the cochlear nerve. To examine this phenomenon, a few animal studies have been done, but only one (2) has concentrated on primary nerve fiber responses. Our study also involved primary single unit responses, but used an indwelling bi-polar cochlear electrode pair--a system more nearly comparable to some of those being used clinically. To facilitate these experiments, special techniques were developed to minimize stimulus artifact picked up by the microelectrodes.

Electrical stimulation threshold tests show that, above about 200 Hz, thresholds vary approximately as frequency raised to the 0.7 power. This behavior is markedly different from the sharply-peaked tuning curves seen with acoustical stimulation. Thus it is probable that the responses seen in these experiments resulted from direct action of the current on excitable tissue and not from an "electrophonic" effect. Other electrical stimulation results reveal that the dynamic range available from electrically induced responses is severely limited when compared to that obtainable from auditory stimulation, and that there is strong synchronization of responses with individual current stimulus cycles.

References

1. D. C. Teas, T. Konishi, and J. S. Wernick (1970). J. Acoust. Soc. Am. 47:1527-1537.
2. E. Moxon (1971). Neural and Mechanical Responses to Electrical Stimulation of the Cat's Inner Ear, Ph. D. dissertation, Massachusetts Institute of Technology.

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**ELECTRICAL STIMULATION OF THE
PERIPHERAL AUDITORY SYSTEM**

**Final Report
National Science Foundation Grant GK32653**

**by
H. N. Munnally**

**School of Electrical Engineering
Georgia Institute of Technology
September 1974**

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SUMMARY

Alternating current electrical stimulation was applied through electrodes implanted in the basal turn of guinea pig cochleas. Responses from primary auditory nerve fibers were detected with glass microelectrodes and recorded on magnetic tape for off-line digital analysis. Special artifact cancellation techniques were used to reduce cross-talk between the stimulation and recording systems. With stimulation frequencies below about 1 KHz, electrical responses are similar to acoustic responses in that they are phase locked to individual stimulus cycles. However, the spike occurrence times tend to be less widely dispersed than with auditory stimulation. With higher stimulus frequencies, fibers respond with a constant firing rate not related to the stimulus frequency. This rate can vary between about 100 and 500 spikes/sec. It decreases with frequency and increases rapidly with level to yield a narrow dynamic range as compared with acoustic response. It is concluded that the responses recorded result from the direct action of the stimulating current on nerve fiber endings rather than from an electrophonic effect or from current effects on hair cell potentials. These results bear some implications for development of cochlear electrical implants in humans.

STATEMENT OF POTENTIAL APPLICATIONS
TO ENGINEERING AND TECHNOLOGY

The restoration of some degree of hearing, or at least auditory sensation, to the profound sensory deaf has been the goal of a number of workers who have applied various forms of electrical stimulation to the auditory system. The present study was undertaken to characterize the responses of primary auditory nerve fibers to alternating current stimulation applied through electrodes located in the basal turn of the cochlea. It would not be accurate to state that sufficient data were developed in this research to specify completely the engineering design of the optimum cochlear stimulator, but insights have been gained as to the potential usefulness and limitations of cochlear electrostimulation. In particular, the results seem to support the notion that complicated multi-electrode implants are no more likely to yield satisfactory results than a single electrode or electrode pair.

DESCRIPTION OF THE RESEARCH AND RESULTS

Introduction

The first recorded example of the application of electric currents to the peripheral auditory system probably dates back to Volta (1800). Since that time, a number of investigators (Andreev, et al., 1935; Stevens, 1937; Stevens and Jones, 1939; Jones, Stevens, and Lurie, 1940; Flottorp, 1953; Djournio, Eyries, and Vallancien, 1957 a and b; Djournio and Eyries, 1957; Doyle, Doyle and Turnbull, 1964; and Simmons, Mongeon, and Lewis, 1964) have studied various aspects of electrical stimulation of the organ of Corti or the eighth nerve itself as a possible treatment for sensory deafness. These studies have been reviewed by Simmons (1966), Moxon (1971), and Sonn (1972).

The emergence of integrated electronic circuitry within the last few years has provided new impetus for clinical experimentation with techniques of cochlear stimulation. Indeed, world-wide interest has developed to the point that an international conference on electrical stimulation of the acoustic nerve as a treatment for profound sensorineural deafness in man was held in June of 1973 at San Francisco. The several groups now pursuing this type of research each utilize different electrodes, electrode placements, and electrical signal processing methods -- which have yielded differing degrees of success. The present developments are now briefly outlined.

Michelson (1971 a and b) implanted a bipolar electrode within the scala tympani in four patients with profound sensory-neural loss. The

electrode consisted of two gold wires imbedded in a silicone rubber mounting which was molded to fill almost completely the scala tympani thus holding the wires snugly against either side of the basilar membrane for about 10 mm of the length of the basal turn. Later results from that study (Merzenich, et al., 1973) indicated that with sinusoidal stimuli, the hearing threshold for one subject rose from about 10 mv (rms) at 100 hz to about 500 mv (rms) at 10 Khz. (Another subject was about 10-db less sensitive.) However, the range in which pitch discrimination could be obtained was limited to frequencies below 400-600 hz, and the useful dynamic range of the system was about 15 db. The stimulating waveforms in this study were derived by direct conversion of acoustic signals into analogous electrical signals.

House and Urban (1973) reported a system in which a single stimulating electrode wire is inserted about 20 mm into the scala tympani, with a remotely located indifferent electrode. The response threshold at 90 hz was 300 mv. The interesting aspect of this work, though, is that by trial and error, it was finally decided that optimal speech recognition was obtained when the signal applied at the electrode consisted of a 16 Khz carrier 90 per cent amplitude modulated by speech-produced signals. No details on threshold versus modulating frequency or dynamic range were reported; but their patient (who was totally deaf) has used the system since May, 1972, and can carry on limited conversations (even over the telephone) with it.

Another study involving application of currents directly to the human cochlea has been reported by Walloch et al. (1973). In this case, a platinum-iridium ball was placed on the round window of a normally-

hearing volunteer. There was initially some difficulty with the electrode placement, but a more satisfactory arrangement was finally obtained and described by Vernon (1973). Results were reported for sinusoidal stimuli with and without amplitude modulation, but there were few quantitative details on thresholds and dynamic range.

In addition to the clinical results reported thus far, considerable effort has been made in related animal work. In their report mentioned above, Walloch et al. also investigated the cortical evoked responses in guinea pigs when the cochlea was stimulated with currents driven via platinum-iridium electrodes inserted into holes drilled in the cochlea. They found the best electrode configuration to be a bipolar pair placed in the scala tympani of the basal turn (one electrode near the round window, and the other about 4 mm apical). With such a placement, thresholds for cortical evoked responses to electrical tone bursts were usually found to be less than 45 μ A for frequencies up to 10 KHz. The responses were still present after acoustic trauma sufficient to render the ear totally unresponsive to sound, and they were also present in ears suffering from drug-induced damage.

Based on experience with modiolar electrodes for direct eighth nerve stimulation in man (Simmons, 1966), Simmons and Glatcke (1972, 1973) made a comparison between the stimulation effects from electrodes in the modiolus and the scala tympani. They used only pulse stimulation and found that the electrical threshold for direct auditory nerve stimulation was about half an order of magnitude less than that for stimulation through electrodes in the scala tympani. Responses were measured at the round window and within the contralateral inferior colliculus.

Animal work in cats with the indwelling cochlear electrode system used clinically by Michelson has been reported by Merzenich et al. (1973). Like Simmons, he chose the contralateral inferior colliculus for a single unit recording site as a means of artifact reduction. He found that most units had their greatest sensitivity at about 100 hz and became less sensitive for lower and greater frequencies -- in sharp contrast to the tuning curves seen for normal acoustic stimulation (Kiang et al., 1965). The most sensitive units were those which originated from the region of the organ of Corti in direct contact with the bipolar electrode array. Such units exhibited thresholds (at 100 hz) of about 10 mv (rms), in good agreement with the clinical studies mentioned above. At 10 Khz, thresholds were about 300 mv (rms). The unit responses were phase-locked to the stimulus waveform for frequencies up to 400-700 hz, and the dynamic range of most units was about 5 to 30 db above threshold.

It would appear that a most desirable method of studying the effects of cochlear electrical stimulation would be achieved through recording the unit responses of primary auditory nerve fibers in the ipsilateral ear. Such an investigation, using glass microelectrodes, has been reported by Kiang and Moxon (Kiang and Moxon, 1972; Moxon, 1971). In this extensive study, the stimulating artifact problem was attacked by using a differential amplification technique whereby the artifact in the fiber recording system was cancelled with a signal picked up nearby containing only artifact. A drawback of the method was that it required careful "tuning" of the microelectrode amplifier via a negative input capacitance control (Moxon, 1972), so that it was not possible to cancel the artifact successfully in all cases. The responses for

sinusoidal electrical stimulation fell generally into two classes. In the first, analogous electric and acoustic stimuli produced similar fiber response patterns; while the other class produced distinctive electrical responses not found for simple acoustic stimuli. It was concluded that the first class represented the result of an "electrophonic" or "electromechanical" phenomenon, in which the basilar membrane was set in motion by the presence of the alternating current, and the neural structures responded accordingly. The second class of responses was felt to be the result of direct depolarization of peripheral nerve membranes by the stimulating current. The stimulating currents were usually applied via a pair of stainless steel wires, one connected to the round window with a saline-soaked wick, and the other resting on the surface of the cochlea. The impedance of this system was measured as being constant at about 7 K-ohms. for frequencies above a few hundred Hz. Thresholds for sinusoidal current bursts were about 70 μ A (rms) at 10 KHz. Thus, the applied voltage at 10 KHz must have been about five volts, one order of magnitude greater than that required with the intra-cochlear electrode of Merzenich et al. (1973).

Therefore, even though this last study was quite extensive and extremely well documented, it is difficult to compare the results obtained with those from the clinically oriented investigations utilizing intra-cochlear electrodes. Also, the clinically oriented studies used recordings not from primary auditory fibers. With these thoughts in mind, we performed a series of experiments in which the responses from primary nerve fibers would be studied under stimulation from electrodes inserted into the cochlea.

Materials and Methods

Animal Preparation

In this study 55 adult guinea pigs weighing about 300 g each were utilized. Ten animals were used for the training of research assistants in the surgical techniques, and the remainder were used in working out various stimulating electrode configurations and in actually obtaining the experimental data. The animals were anesthetized with sodium pentobarbital (50 mg/kg) administered intraperitoneally. After a tracheostomy and insertion of a tracheal cannula, respiration was maintained with a constant volume animal respirator. Body temperature was monitored rectally and used to control a heating blanket so that normal temperature was maintained. The skull was immobilized in a stereotaxic frame and the auditory nerve was exposed via a surgical procedure almost identical to that first used by Tasaki (1954). Details of the surgical approach and much of the electronic instrumentation are documented by the author in earlier work (Nunnally, 1971). The end result was that a 0.5-mm hole was drilled near the base of the cochlea to intersect the auditory nerve bundle within the internal auditory meatus.

Acoustic Stimulus Generation

Acoustic stimuli were delivered with a B & K 4145 capacitor microphone operated as an earphone and mounted in one of the ear bars of the stereotaxic frame. This system was calibrated so that sound levels in db (re. $0.0002 \text{ dynes/cm}^2$) could be obtained from the voltage applied to the earphone. Stimulus waveforms were either continuous tones or tone bursts (2.5-ms exponential rise-fall time) of controllable duration, repetition rate, frequency, and intensity. Each tone burst of a given

series always began with the same relative phase. As a routine part of the experimental protocols, the cochlear microphonic (CM) response to a continuously swept tone was obtained with a recording wave analyzer at various times throughout the procedures. Measurement of CM was accomplished with a 25- μ nichrome enamel-insulated wire (scraped at the tip) inserted into a 30-40 μ hole drilled in the scala vestibuli of the basal turn of the cochlea.

Electrical Stimulus Generation

Electrical stimuli were derived from the acoustic waveform generating equipment and delivered to stimulating electrodes through an isolating system as indicated schematically in Figure 1. The stimulating current, i_s , was monitored with the voltage V_m , which was proportional to i_s according to the relation:

$$i_s = V_m \times (.000250 \text{ amps/volt})$$

Data Acquisition, Recording, and Processing

The primary auditory nerve fiber responses were detected with glass microelectrodes filled with 3M KCl.* If electrical stimuli were used, an artifact reduction technique (discussed below) was employed before the action potential spikes were recorded on one channel of a high-fidelity analog tape recorder after high- and low-pass filtering. On the other channel was simultaneously recorded a pulse train to mark the beginning

* Signals were amplified at first with a specially constructed vacuum tube amplifier, but the last few experiments employed an Instrumentation Laboratories "Picometric" solid state amplifier.

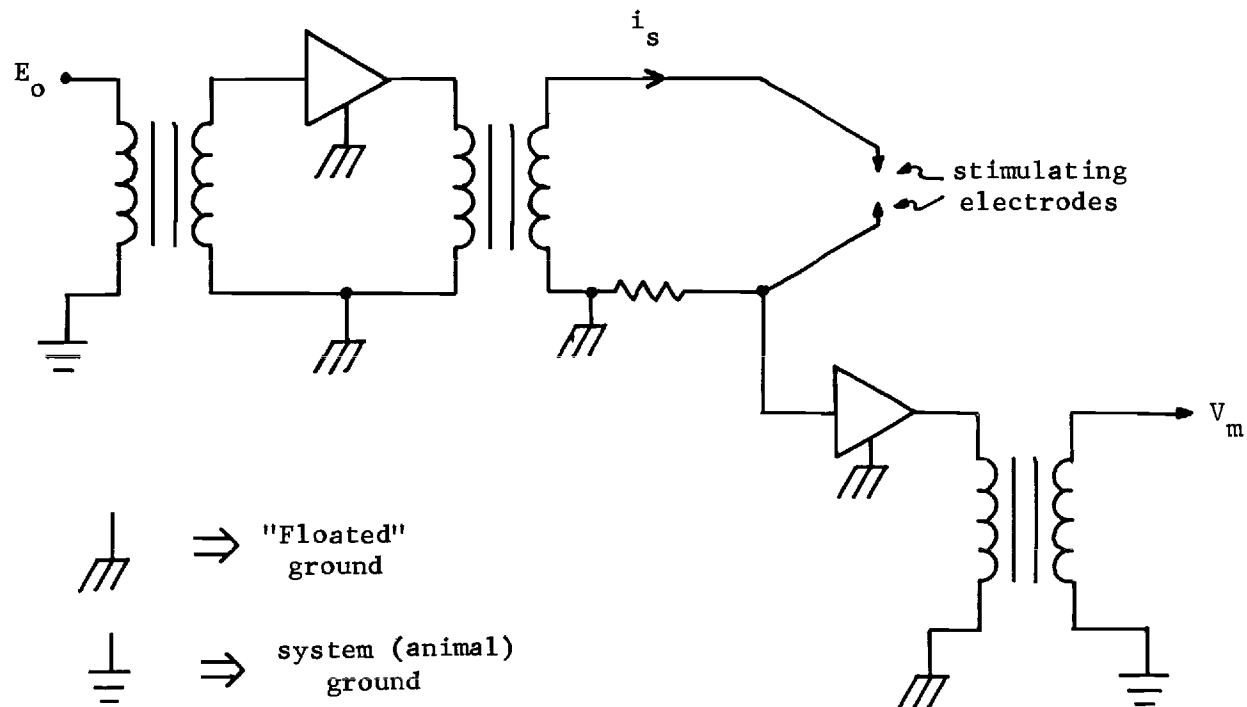


Figure 1. Block diagram of electrical stimulating system.
 E_o is the electrical output of the acoustic waveform generator; V_m the current monitor voltage; and i_s is the stimulating current.

of each acoustical or electrical tone burst. For off-line processing, the nerve signals were passed through a level detector, the output of which caused a GRI 909 mini-computer to read the spike occurrence times from a clock reset with the timing pulses of the other tape channel. These event occurrence times were then recorded on digital magnetic tape using a Kennedy 1600 incremental tape recorder. These data were input to a Univac 1108 computer for which programs had been written for computing and plotting both post stimulus time (PST) and inter-spike interval time (ISI) histograms of the nerve fiber response.

Stimulating Electrodes and Placements

A number of different stimulating electrodes and electrode placements were tried in the duration of the study. At the beginning, it was felt that an electrode similar to that used by Michelson (Michelson, 1971 a and b; Merzenich, 1973) should be used because of the low electrical thresholds reported clinically with it. However, it was decided that to make a guinea pig version of this electrode would have required too great a portion of the time allotted for this study. Furthermore, such an electrode would have to be placed through the round window. Close examination revealed that such a placement technique would probably have to be accomplished by going through the ear drum itself; and since we were interested in recording acoustical and electrical responses from the same units, this method would be impractical.

The next procedure considered was to place a pair of ball electrodes on either side of the basilar membrane through an oblique round window penetration. Even though this would have been technically possible, the idea was not actually pursued for two reasons. First,

it was feared that such a procedure might damage the basilar membrane complex; and secondly it was felt that only a small number of nerve fibers would respond due to the small size of the resulting current spread. Therefore three other methods were developed, the last of which was the most successful in terms of simplicity of application and the stimulation of nerve units.

The first method involved drilling a large opening (approximately 1 mm x 2 mm) in the scala tympani of the basal turn and inserting a bipolar electrode. It has been shown by Kohlloffel (1971) and verified in our own work that such an opening can be made without seriously affecting the ear's response as reflected in CM recordings. The electrode consisted of two, 1.2-mm lengths of 0.002" wire mounted side by side about 1 mm apart on a 0.5-mm Lexan plastic base. The assembly was inserted through the scala tympani hole, so that the two wires were running more or less parallel with the basilar membrane for the 1.2 mm of their length. Gold, silver, and platinum wires were used, but we were never able to find units which responded to currents delivered with this system. In addition, it proved extremely tedious to position and maintain this assembly.

In an effort to place the stimulating current closer to the basilar membrane, a second method was attempted. Again, a large opening was drilled in the scala tympani, but the stimulating electrode was simply a 2-mm length of silver or platinum wire (0.003" in diameter) formed into a circular segment with radius matching that of the basilar membrane spiral in the basal turn. This electrode was carefully placed (either manually or with a manipulator) directly in the basilar membrane. This procedure did produce results in one animal, but in others the placement procedure caused rupture of the basilar membrane. At about this

time in the study, the results of Walloch et al. (1973) were published and it was decided to adapt their electrode system, which was simpler than any we had tried to date.

In this last method, two 0.006" holes were drilled in the scala tympani of the basal turn -- one very near the round window and the other about 3-4 mm apical. Into each hole was inserted a 0.005" wire electrode insulated with epoxy paint except for a 1.2-mm segment at the tip. The first attempts with this procedure utilized platinum wire, but for reasons discussed later, we changed to silver wires which were chlorided using the procedure given by Silver (1958).

Artifact Reduction

The greatest instrumentation problem in an experiment of this type is cross-talk (artifact generation) between the electrical stimulating system and the ultra-high impedance, high gain microelectrode nerve response pick-up system. Even using an isolated stimulator, one still measures cross-talk which is many times greater than the spike potentials of interest. The approach we took for this problem was to use a differential amplification technique whereby a signal containing only cross-talk (recorded with the CM electrode) is subtracted from the nerve amplifier signal, which consists of both cross-talk and spike potentials. The problem, however, is that the cross-talk in the nerve spike channel generally has a different phase than that in the other channel because of the input capacitance of the microelectrode. Therefore, a special phase shifting circuit was built so that the amplitude and phase of the artifact from the CM electrode could be precisely and conveniently matched to that in the nerve channel before differential

amplification. A block diagram of the overall system is given in Figure 2 and a circuit diagram of the phase shifter is given in Figure 3. The phase shifter operates in the following manner. The input signal, V_{in} , which consists of artifact only, is buffered and used to drive a center-tapped audio transformer. The transformer output, noted as $V / 0^\circ$ in the Figure 3, is applied to a sine-cosine potentiometer, which produces two signals, $V \sin \theta / 0^\circ$ and $V \cos \theta / 0^\circ$, where θ is the potentiometer shaft angle. These signals are then fed to a series RC circuit to produce the output V_{out} . It can be shown that if RC is picked to be $1/2\pi f$, where f is the excitation frequency, then

$$V_{out} = \frac{V}{\sqrt{2}} \angle \theta - 45^\circ$$

Thus, the output phase can be completely controlled by the potentiometer setting without affecting the output magnitude. The restriction on RC requires that either R or C be variable if more than one excitation frequency is to be used. Thus, R was set at $100 \text{ K}\Omega$ and ten capacitors were available via a selector switch to allow operation at 0.05, 0.1, 0.2, 0.5, 1.0, 2.0, 5.0, 10, 20, and 30 KHz.

A constraint of the cancellation technique is that for good artifact cancellation, the artifacts must be undistorted sine waves. This constraint necessitated the use of chlorided silver stimulating electrodes, as discussed later. Also, the dynamic range of the micro-electrode amplifier had to be great enough to pass the artifact without clipping. When stimulation frequencies were higher than the band-width of the nerve spikes themselves (about 1 KHz), the cross-talk was further reduced by additional low-pass filtering.

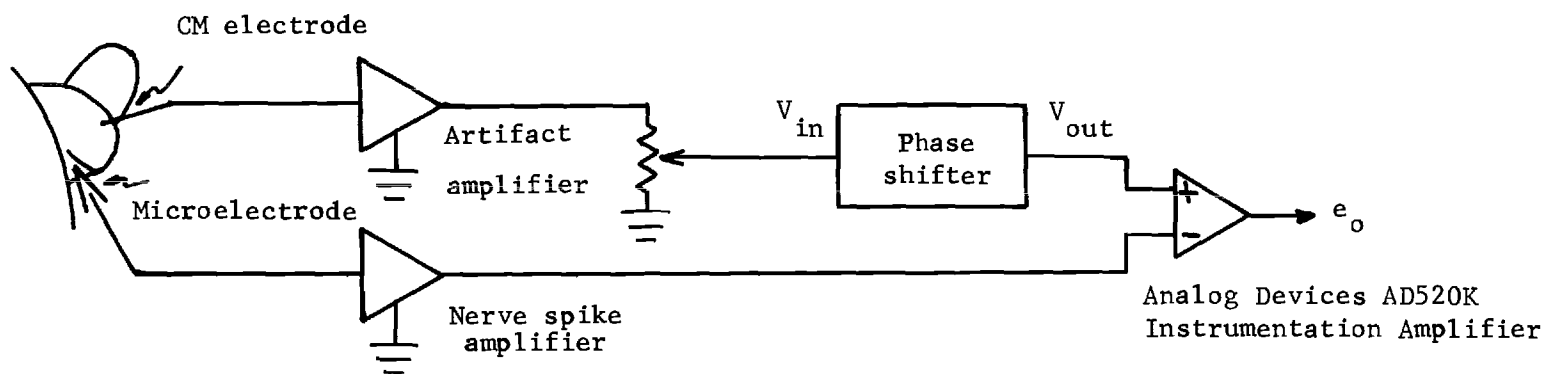


Figure 2. Block diagram of artifact reduction system.

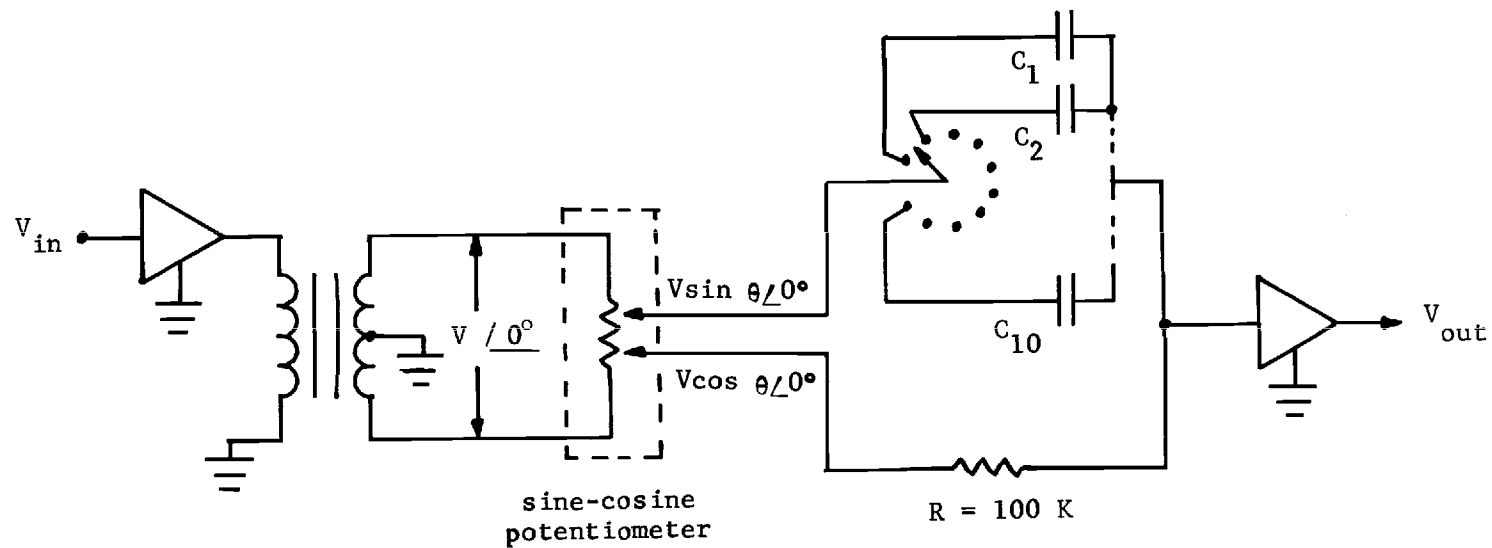


Figure 3. Circuit diagram of phase shifter. Sine-cosine potentiometer is Technology Instrument Corp. #RV1½-S2. Potentiometer shaft

angle is θ . Capacitor values specified by $10^5 C_k = \frac{1}{2\pi f_k}$,

$k = 1, 2, \dots, 10$. Values for f_k are 0.05, 0.1, 0.2, 0.5, 1.0, 2.0, 5.0, 10, 20, and 30 kHz.

Results

The primary results of this research involve the characterization of the response of primary auditory nerve fibers to alternating current electrical stimulation. That information is described below. In obtaining the data, insight was also gained concerning characteristics of the stimulating electrodes used in the experiments. This information should be useful to others in future experiments in this area, so it has been included in the Appendix.

During the experimental phase of the study, 17 preparations yielded animals producing recordable sound-evoked single unit nerve fiber potentials. In all, 201 fibers were contacted and studied for varying lengths of time. For 178 fibers, the acoustic thresholds were found by listening to the spike discharges produced as the ear was stimulated with tone bursts (50 ms duration, 10 per second) and determining the frequency for which the nerve responded with the minimum stimulus. The frequency so determined is the unit's characteristic frequency (CF) and the corresponding level is its acoustic threshold (AT). Figure 4 is a scatter diagram of these thresholds as a function of CF for all 178 fibers. The diagram compares quite favorably with a similar figure for guinea pig auditory units given recently by Evans (1972). However, it is apparent that in general the thresholds for the animals studied toward the end of the series (numbers 329-344) are higher (by 10-20 db) than those from the earlier experiments. The reason for this is unclear at this time, as the same operative techniques were employed in all animals. This situation is unfortunate in light of the fact that almost all the data from units which responded to electrical currents came from this latter group. Thus we cannot be assured that the electric responses obtained represent the true response of an uncompromised cochlea to electric currents.

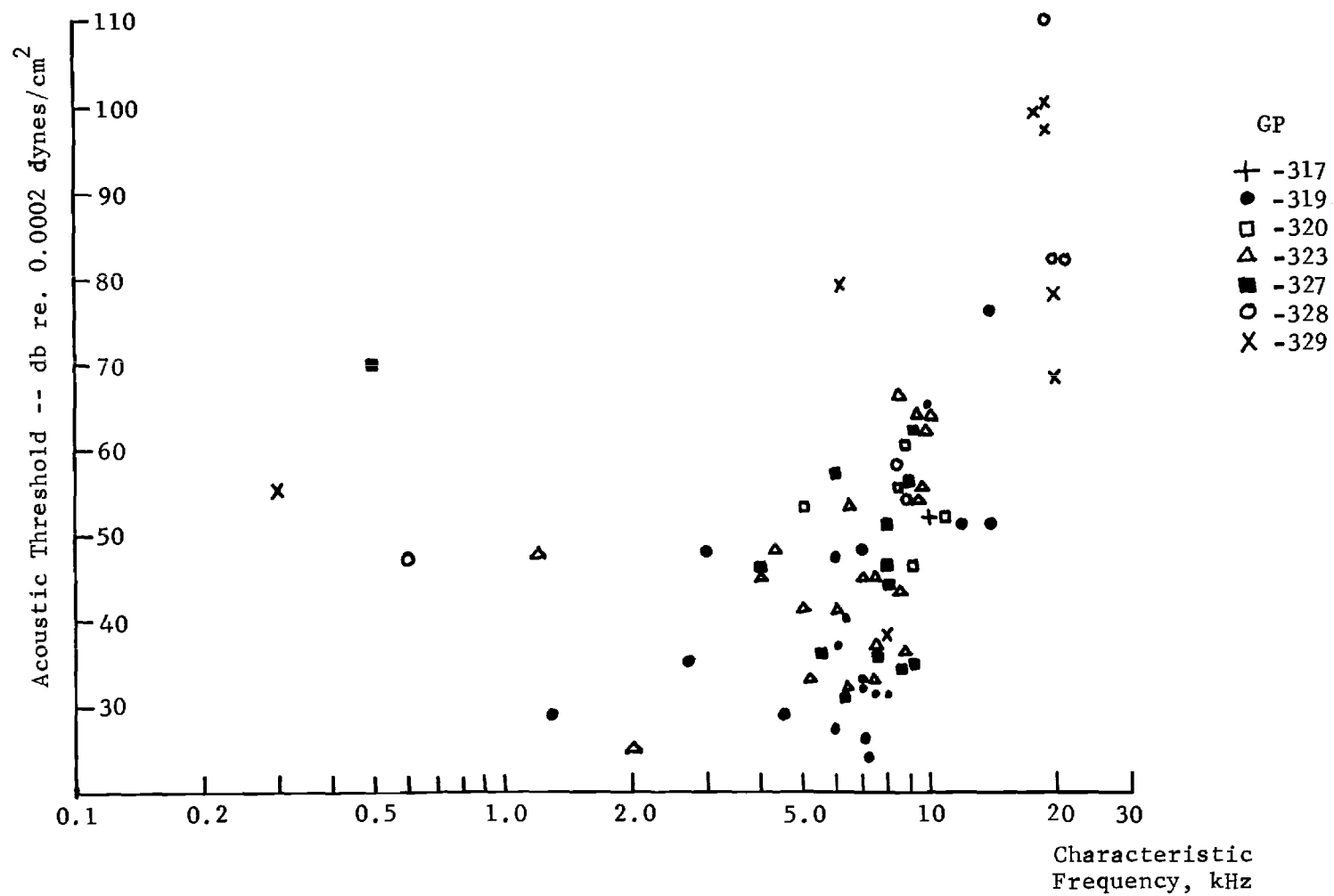


Figure 4. Scatter diagram of acoustic threshold vs. characteristic frequency for 178 units.

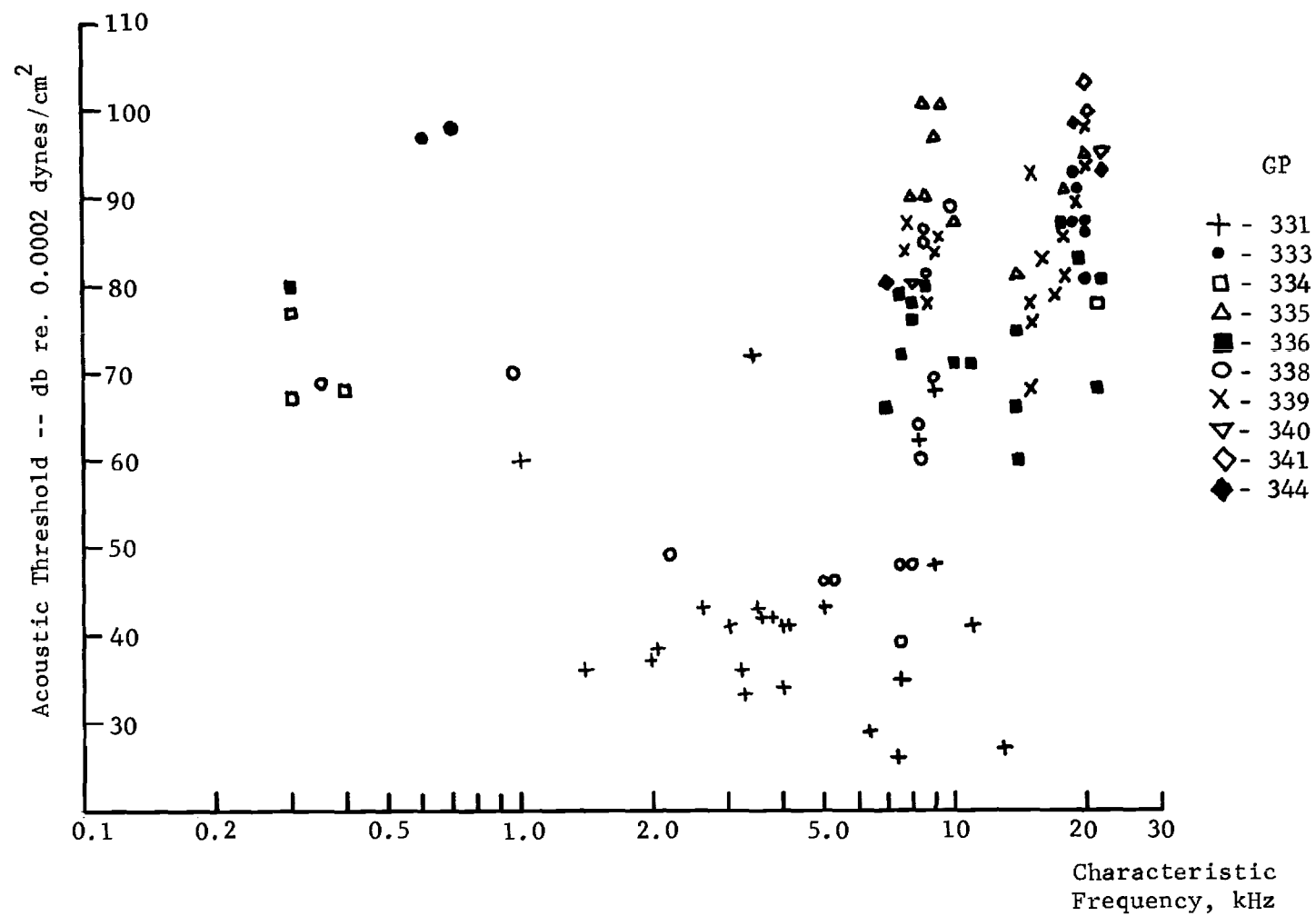


Figure 4. (continued).

Three experiments were performed to characterize the effects of cochlear electrical stimulation. These were (1) the determination of electrical threshold as a function of frequency, (2) study of the effect of stimulus frequency on electric response patterns, and (3) study of the effect of stimulus intensity. (In the discussion to follow, the current intensities given will be rms values.)

Electrical Stimulation Thresholds

Electrical stimulation using one of the electrodes described earlier was attempted in 18 preparations. In the first five, the Lexan-based electrode was employed, but responses were found only in two animals (2 units in each), both of which exhibited unusually sensitive acoustic thresholds. This fact, together with the result that electrical stimulation was achieved only at frequencies near the units' acoustic CF's strongly suggests that this response was electrophonic in nature (Moxon, 1971).

After it became clear that this electrode would not give satisfactory results, the procedure of placing a circular wire electrode directly on the basilar membrane was pursued. Seven animals were tried using the silver or platinum wires placed either on the "hook" portion of the basilar membrane or on a more apical segment still in the basal turn. The sixth animal did produce one electrophonic response. As indicated before, the main difficulty with this method is the probability of damaging the basilar membrane. However, the seventh animal produced a few units which responded to current bursts in a non-electrophonic manner. For these units, electrical burst thresholds (EBT) were determined (as frequency was varied) using techniques analogous to those for acoustic thresholds. The

results are summarized in Figure 5. Note that the curves plot on log-log coordinates as approximately straight lines with the same slope, indicating an exponential dependence of threshold on frequency. In this case, threshold appears to be proportional to frequency raised to the 0.7 power. The threshold at 100 Hz is about 70 μ a rms, in very good agreement with Moxon's (1971) data. However, Moxon interprets his curves as giving a linear, rather than exponential, threshold characteristic.

The remaining six animals from which electrical responses were obtained all employed the electrode placement described by Walloch *et al.* (1973). Results of threshold-frequency measurements on four of these animals are shown in Figure 6, from which it is clear that this electrode placement gives results consistent with those from electrodes placed directly on the basilar membrane.

Effects of Changing Electrical Stimulation Frequency

Data suitable for computer reduction to show the effects of changes in electric stimulus frequency and intensity were obtained in three animals. Even though this is a small sample size, we feel the results are valid since all three preparations gave the same characteristics, and those characteristics are generally consistent with results from other investigators. In all these studies the stimuli (acoustic or electric) consisted of 50 msec sinusoidal bursts shaped with a 2.5-msec exponential rise/fall time characteristic. Stimuli were presented at a repetition rate of 10 per second for 30 seconds for each set of experimental parameters.

The effect of altering stimulus frequency is shown clearly in Figure 7, which shows post-stimulus-time (PST) and interspike-interval-time (ISI) histograms for a number of frequencies. The current level in each was set to about 2 db above threshold for the particular frequency.

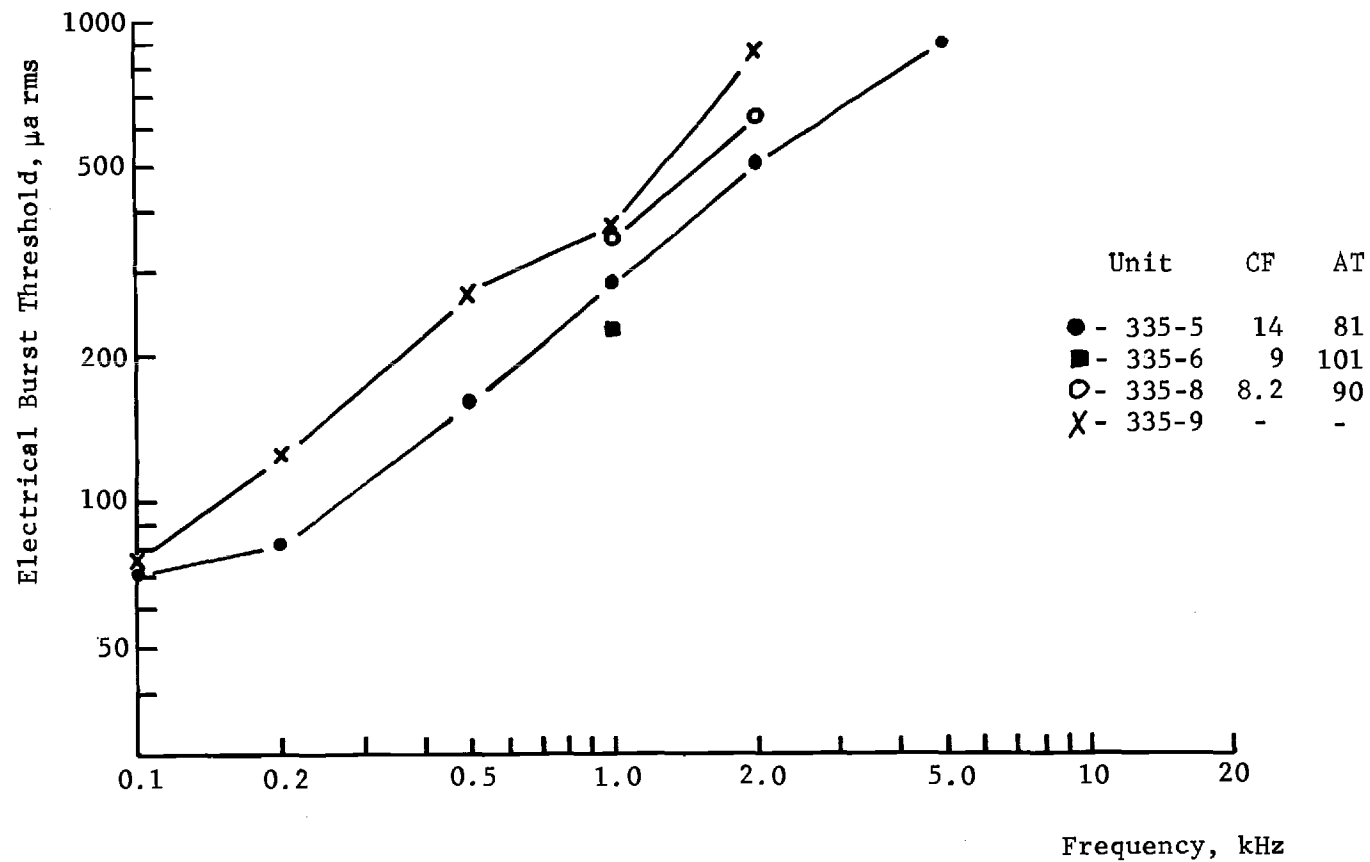


Figure 5. Electrical burst thresholds for four units from guinea pig 335. Acoustic characteristic frequency (CF) and acoustic threshold (AT) are indicated for each unit in kHz and db re. 0.0002 dynes/cm² respectively. Stimulating electrode was circular platinum wire placed on basilar membrane.

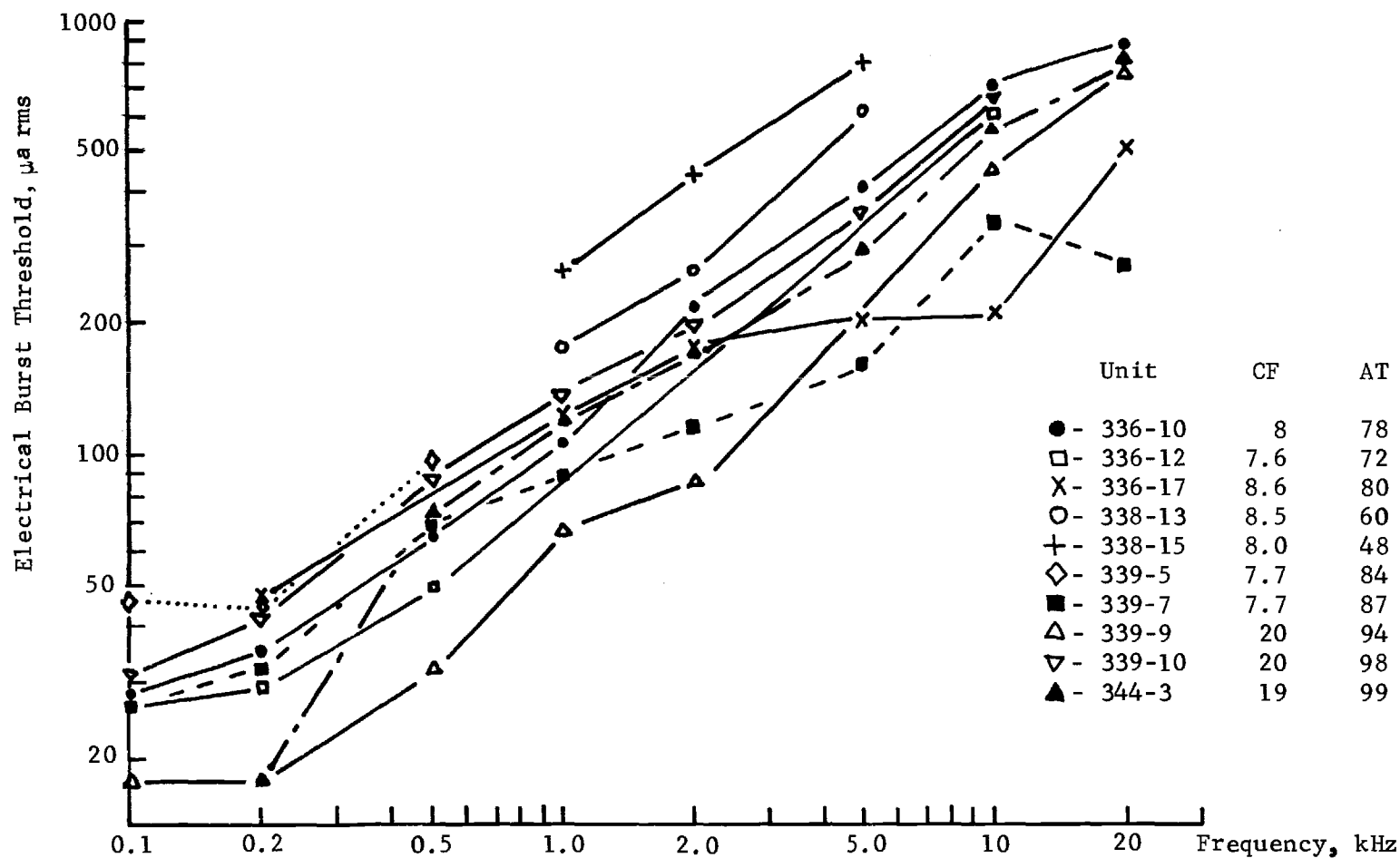


Figure 6. Electrical burst thresholds for guinea pigs 336, 338, 339, and 344. AT and CF as in Figure 5. Stimulating electrodes in each case were 0.005-in. x 1.2 mm wires inserted into scala tympani of basal turn. For 336, 338, and 339, wires were bare platinum. For 344, wires were silver, coated with silver chloride.

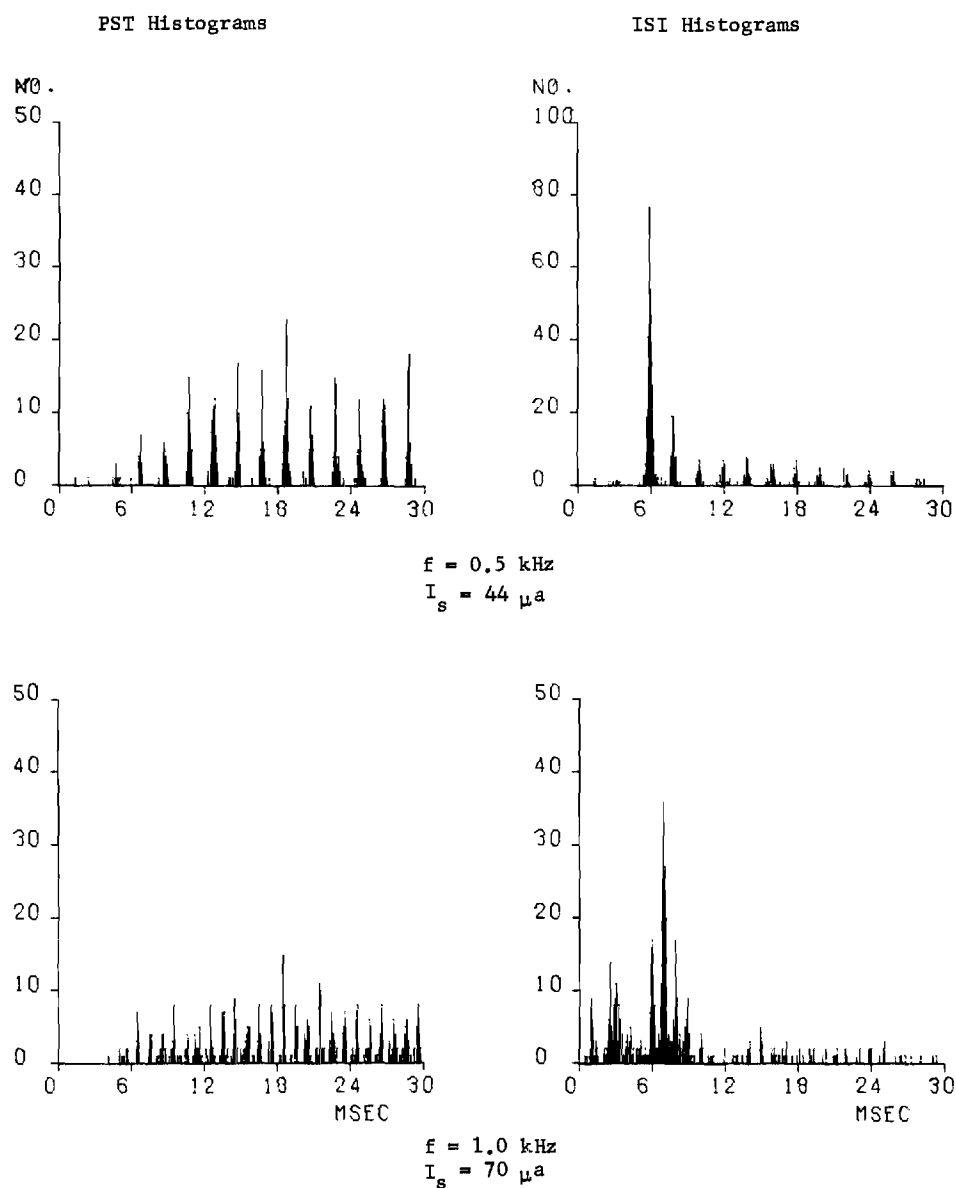


Figure 7. PST and ISI histograms showing effect of changing electrical stimulation frequency. Stimuli: sinusoidal current bursts, duration 50 msec, 10 per second repetition rate, intensity approximately 2 db above threshold. I_s , current level (rms); f , frequency. Histogram resolution, 0.1 msec. Each histogram computed from 30 seconds of data. Unit 344-3, characteristic frequency 19 kHz, acoustic threshold 99 db.

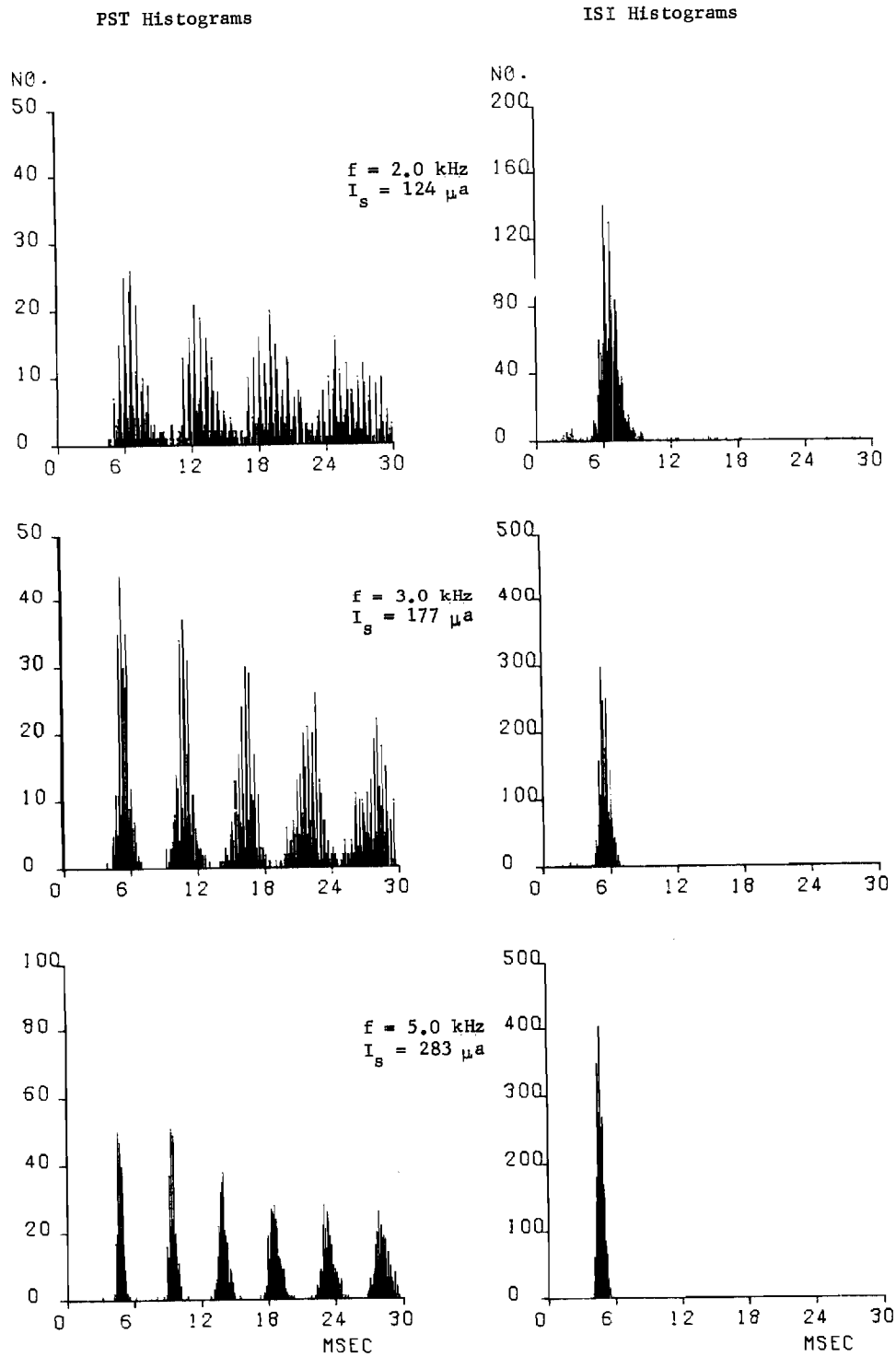


Figure 7.
(Continued)

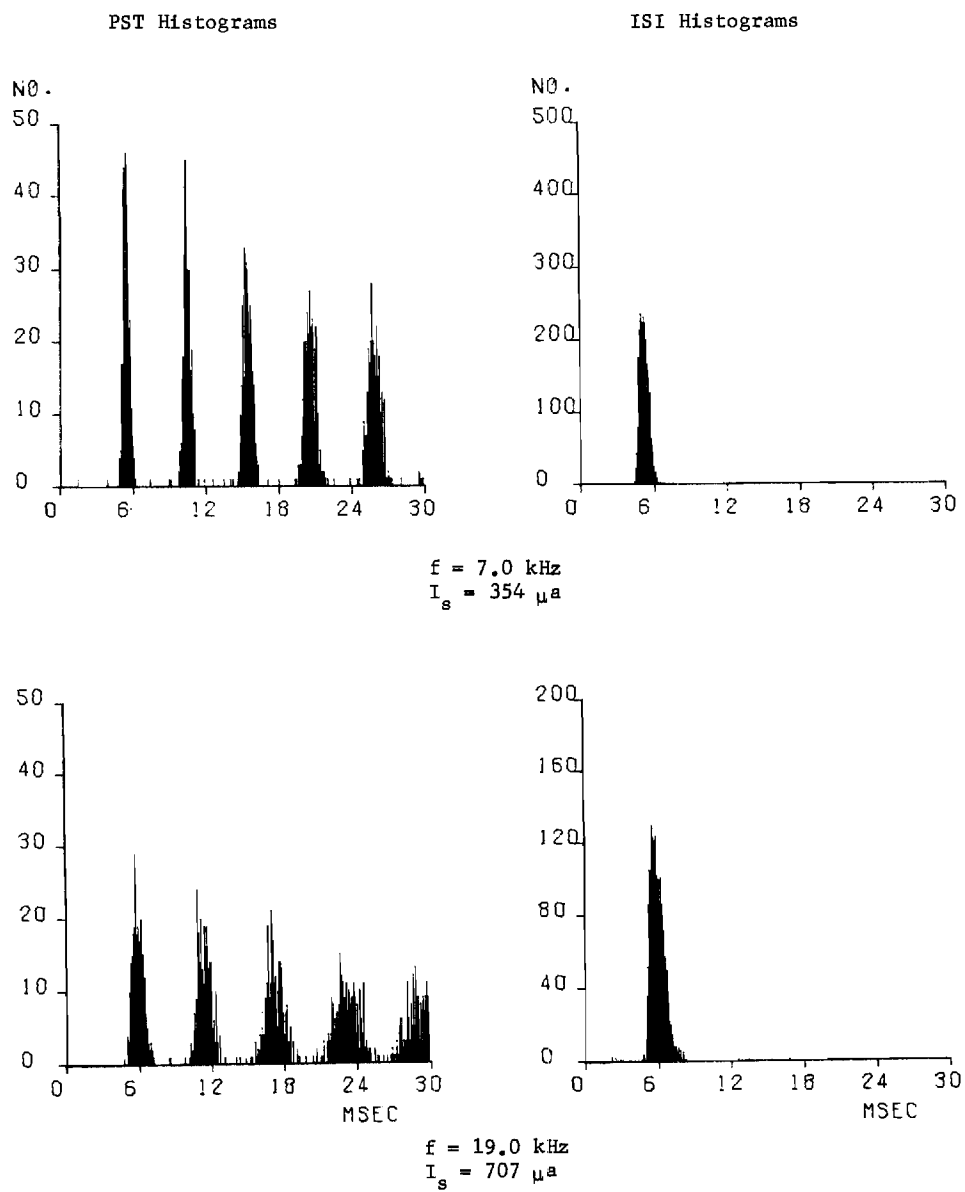


Figure 7.
 (Continued)

This setting was difficult to make exactly since the input/output characteristic for electrical response rises so rapidly near threshold. From the figure we note that for low frequencies (in this case, 0.5 KHz and 1.0 KHz), the PST envelope shows peaks occurring at intervals corresponding to multiples of the period of the stimulus frequency. These responses, then, are "phase-locked" to individual stimulus cycles, even though there is not a response to each stimulus cycle, as shown by the ISI graphs. In fact, the preferred interspike time is 6 msec (3 stimulus periods). Such phase-locking is always seen in auditory nerve fiber response to low-frequency acoustic stimuli (Kiang, 1965; Nunnally, 1971).

When the frequency is increased above about 1 KHz, the character of the responses changes altogether. At 2 KHz, we see there is still clear phase locking, but the responses tend to come in groups separated by about 7 msec. The same behavior is shown at 3 KHz. At 5 KHz and higher, we no longer see phase locking to individual stimulus cycles, but the 6-7 msec grouping of discharges remains. Examination of the PST histograms for high frequency shows the later peaks in each histogram are always broader than early peaks, indicating that successive interspike intervals are independent of each other. Thus the electrical response to sinusoidal current bursts near threshold intensity for all frequencies above about 3 KHz appears to be independent of stimulus frequency and consists of very regular spike trains with a frequency of about 167 Hz.

These data are consistent with the clinical observations of Merzenich et al. (1973) that patients with implanted cochlear stimulators have difficulty with pitch discrimination for electrical stimulation frequencies above about 1 KHz. In that report and in Moxon's (1971) work, results on phase locking derived from cat data were obtained. Both

studies showed that electrical excitation produces phase-locked responses for low frequencies (less than 1-2 KHz). Moxon also found grouping of primary nerve fiber discharges for higher frequencies. On the other hand, such grouping was not apparent in the inferior colliculus data given by Merzenich and his associates.

Even though low-frequency electrical and acoustic stimulation do give similar, phased-locked results, direct comparison of responses to both modalities in the same unit indicates at least one significant difference, as shown in Figure 8. Here, histograms are given for a unit excited electrically and acoustically at 1 KHz with levels adjusted so that the total number of nerve firings is about the same in each case. Note the PST graphs are almost identical, but the ISI histograms are much less spread out for electrical excitation than for acoustic stimulation. This shows the electrical response is characteristically more regular than the highly probabilistic response typically seen in auditory stimulation. Such regularity of electrical response was seen in all the electric response data.

Effects of Changing Electrical Stimulation Intensity

Figure 9 shows the effect of changing the stimulus current level at a constant burst frequency of 5 KHz. Several characteristics of this response should be noted. One is the rapid change in fiber response level as current intensity is changed near the threshold value. The first histogram in Figure 9 represents 1716 responses for an input current level of 250 μ a (near threshold). The second graph contains 3405 responses for 327 μ a, so that a 2 db change in input caused the output to increase by a factor of 1.98. Similar results were obtained for other frequencies and

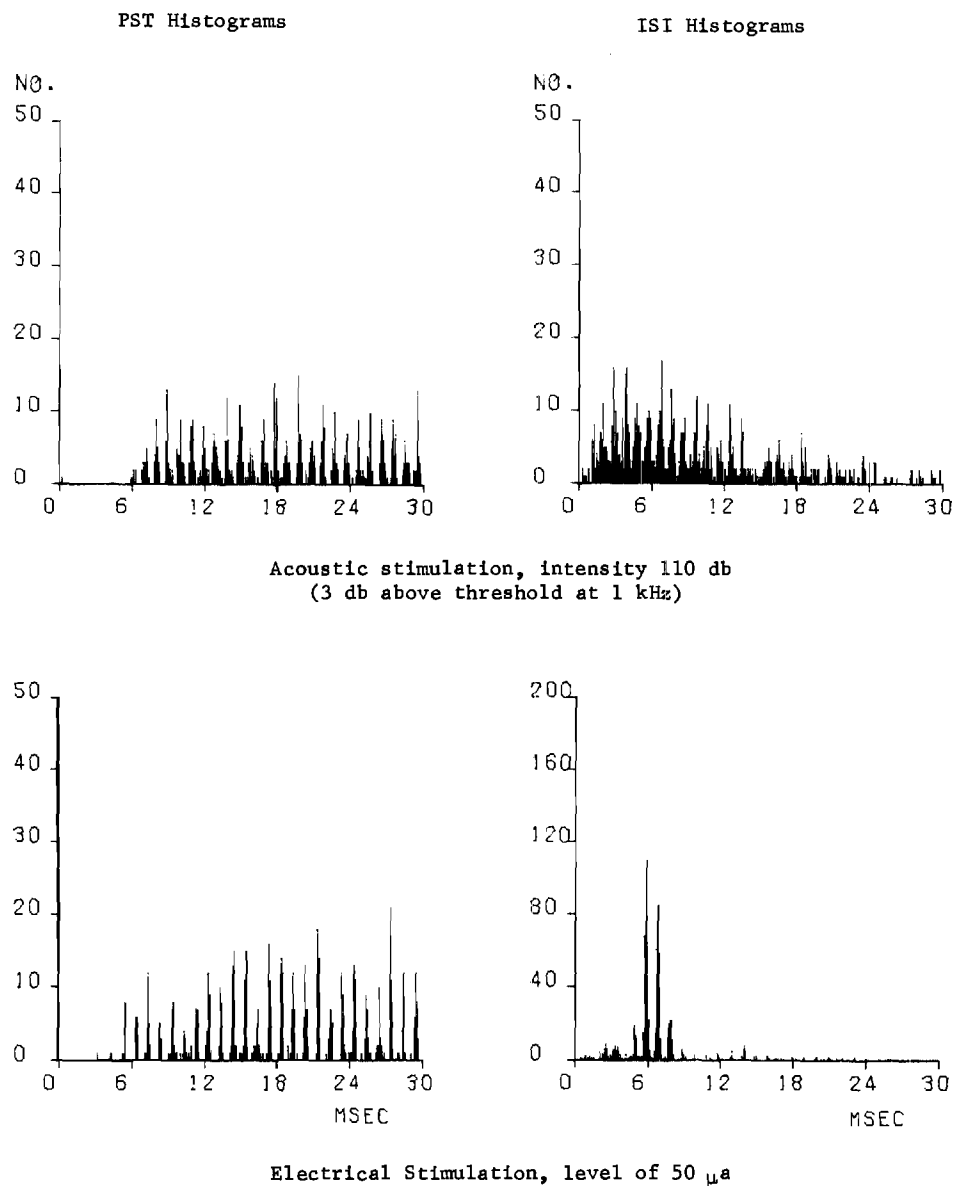


Figure 8. Comparison of electrical and acoustic responses in the same unit. Stimuli: sinusoidal current and acoustic tone bursts, frequency 1.0 kHz, duration 50 msec, 10 per second repetition rate. Histogram resolution, 0.1 msec. Each histogram computed from 30 seconds of data. Unit 344-2, characteristic frequency 19 kHz, acoustic threshold 94 db.

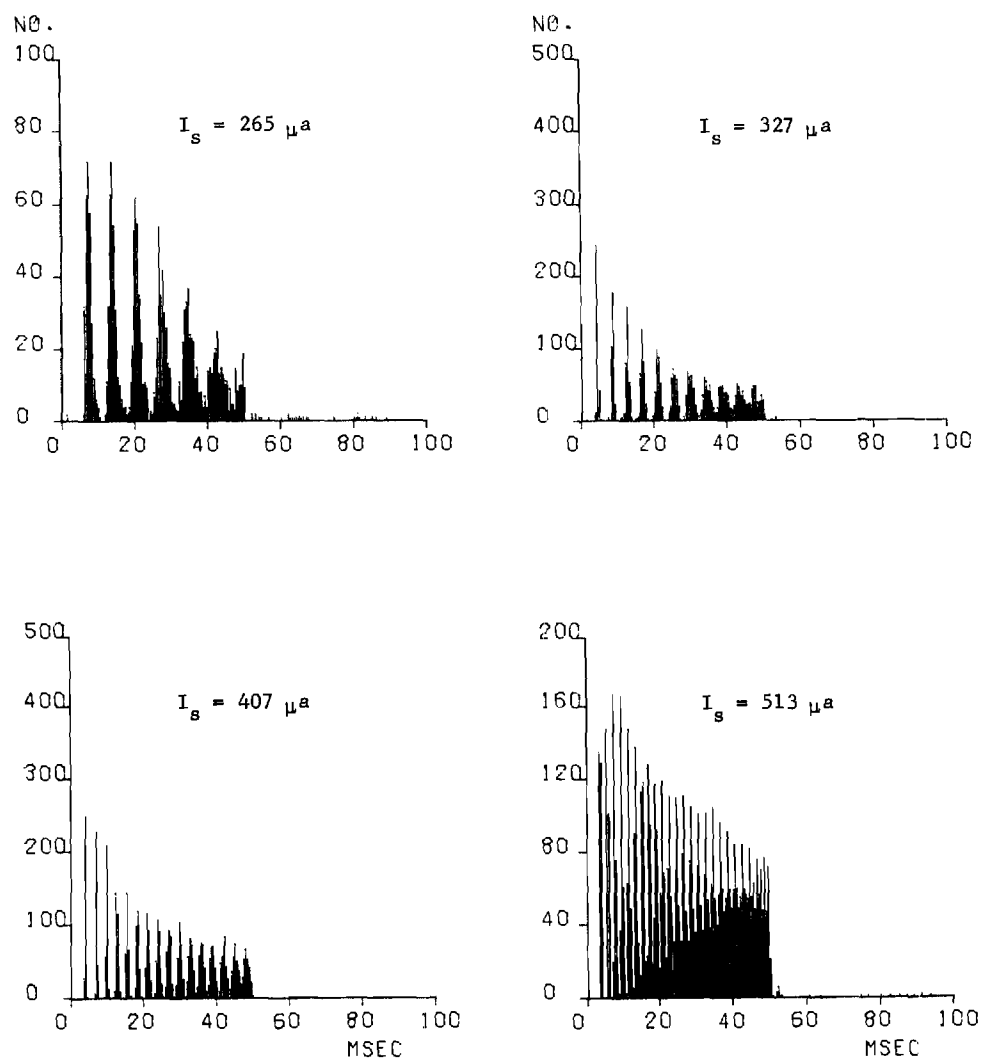


Figure 9. PST histograms showing effect of changing electrical stimulation intensity. Stimuli: sinusoidal current bursts, duration 50 msec, 10 per second repetition rate, frequency 5 kHz. I_s , current level (rms). Histogram resolution 0.5 msec. Each s , histogram computed from 30 seconds of data. Unit 344-3, characteristic frequency 19 kHz, acoustic threshold 99 db.

are summarized in Figure 10. In this figure, histogram data for the unit of Figure 9 has been converted to spike rates for electrical stimuli at 2, 5, and 19 KHz. Note that at higher frequencies, more current is required to produce a given spike rate. This is consistent with the fact that electrical thresholds also increase with frequency. Also included in the figure is an intensity function for acoustic stimulation at 19 KHz from which it is clear that the current response characteristic is much steeper for electrical than for acoustic stimulation. It is difficult to be more precise about the relative effectiveness of acoustic versus electrical stimulation near threshold, since acoustic intensity functions vary widely among different fibers (Kiang, 1965).

Figure 10 also shows that electrical stimulation can result in spike response rates on the order of 300 to 500 spikes/sec. This is much higher than the 200 spikes/sec upper limit normally seen in acoustic stimulation (Kiang, 1965; Nunnally, 1971). It is not known if the spike rates could have been driven even higher with greater currents, since stimulus cross-talk prevented analysis for the higher levels.

Another feature seen in Figure 9 is that the grouping of discharges at preferred firing times (not related to the stimulus frequency) changes with increasing current intensity. It has already been pointed out that grouping occurs whenever the stimulus frequency is more than about 2-3 KHz. The data of Figure 9 indicate that grouping occurs with each current intensity, but that the time interval separating preferred firing times decreases with increasing current levels. Also, ISI histograms for this data (not shown) are uni-modal, so that the response to increasing electrical stimulation at a constant frequency consists of a regular discharge

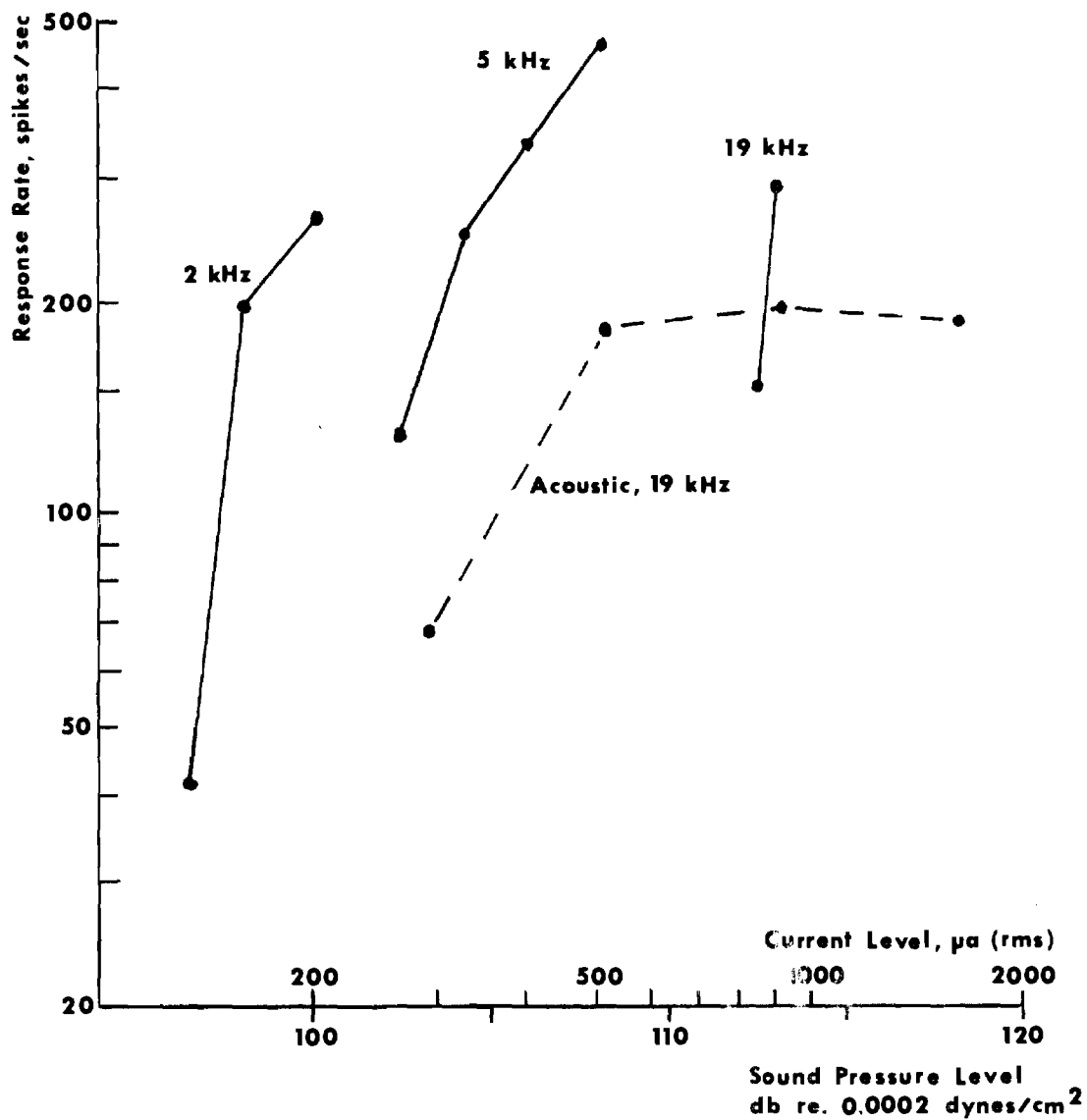


Figure 10. Intensity functions for acoustic and electrical responses in the same unit. Acoustic stimulation at 19 kHz; electrical stimulation at frequencies indicated. Rates computed from responses occurring during application of 50-msec stimuli at 10 per second repetition rate for 30 sec. Unit 344-3, characteristic frequency 19 kHz, acoustic threshold 99 db.

at a rate which grows with increasing intensity.

Summary of Electrical Response Characteristics

From the data collected in this study, the responses of primary auditory nerve fiber responses to short bursts of sinusoidal current in the cochlea may be summarized as follows. The threshold of response is approximately proportional to stimulus frequency raised to the 0.7 power. This is in sharp contrast to the sharply-peaked tuning curves routinely seen in auditory stimulation (Kiang, 1965; Nunnally, 1971). For stimulation frequencies below 1-2 KHz, electrical responses are phase-locked to individual stimulus cycles, but in a much more deterministic manner than is found acoustically. Nevertheless, near threshold at least, each stimulus cycle does not produce a response. When frequency is increased above 2-3 KHz, stimulus phase locking gives way to a situation in which fibers fire very regularly at a rate which increases with current level for a given frequency. That rate can approach values much higher than the rates which can be observed for normal auditory responses. Finally, the discharge rate decreases with increasing frequency for a constant current level.

Discussion

With the above data in mind, a number of observations can be made.

1. The responses obtained in this study are probably due to direct action of the stimulating current on cochlear nerve fibers. Several considerations bear this out. First, the smooth rise of electrical threshold with increasing frequency represents the same type of behavior found by Hill et al. (1936) in a study of the response of nerve to alternating

current. Secondly, electrically-induced spike rates were found which are much greater than the rates which can occur with normal acoustical stimulation through the action of hair cell potentials on nerve fiber endings. Interestingly, hair cell potentials can be altered by the application of direct currents across the cochlear partition (Nunnally, 1971) so that acoustic sensitivity is changed. In such experiments, though, it was never possible to drive fiber response rates above the maximum levels attained without electrical polarization. Thus, the present alternating current responses must arise by a mechanism that does not depend on events more peripheral than the nerve ending. Finally, it is most unlikely that the current induced responses arose electrophonically--that is by an electromechanical process converting stimulating current to acoustic perturbations in the cochlear fluids. Again, such responses would not exhibit the high spike rates noted above, and they would produce histograms very similar to those derived from acoustic responses.

2. Several characteristics of the current-induced responses carry implications regarding the use of cochlear electrostimulation to provide auditory information for persons with sensory deafness. In electrical stimulation, there are large numbers of fibers firing simultaneously and regularly, so that the normal probabilistic distribution of neural events is lost. In addition, for stimulation in the basal turn, fibers which normally respond to high-frequency acoustic stimulation are being activated. Nevertheless, patients with basal turn cochlear implants can accomplish remarkable pitch discrimination for low frequencies.

(Merzenich et al., 1973). Indeed, for frequencies below about 1 KHz, the electrical responses are similar to low frequency auditory responses in

that stimulus phase locking occurs. That is, the central nervous system can adapt its processing to obtain low-frequency periodicity information from fibers normally most responsive to high-frequency auditory excitation. On the other hand, clinical results of Merzenich et al. (1973) indicate that high-frequency tonal sensations are not obtained through basal turn electrical stimulation. Therefore, it seems likely that low-frequency information is imparted electrically through the discharge cadence (not by a place mechanism), and that no simple electrical stimulus will necessarily yield high-frequency sensations. If this is true, then it is not certain that multi-electrode systems will offer significant speech-discrimination advantages when compared to a simple, single electrode pair system such as that employed in this study. Nevertheless, multiple electrode studies in humans should certainly be undertaken.

House and Urban (1973) reported on clinical results using a multi-electrode system, and they concluded that a single electrode system worked as well, based on the preferences of patients. They finally settled on a system in which the electrical stimuli are derived by AM modulation of the input signals (carrier frequency about 16 KHz). Data from the present study show that at high frequencies, the electrical fiber response rates depend on frequency and level. If the frequency is maintained and the stimulus level increased, the fiber discharge rate will increase. These results could explain the success of the AM modulation techniques in terms of the interaction of fiber discharge rate and stimulus level.

PROJECT PERSONNEL AND THEIR CONTRIBUTIONS

1. H. N. Nunnally, Principal Investigator.

As Principal Investigator, Dr. Nunnally conducted all the project experiments (with the assistance of others), supervised all aspects of the research, analyzed the data, and prepared this report.

2. J. H. Schlag.

Dr. Schlag, Associate Professor, School of Electrical Engineering, provided invaluable aid and assistance by updating the data reduction system and writing the necessary soft-ware to allow conversion of raw analog data into spike occurrence times for recording on digital tape for processing on the 1108 Computer. He also designed the stimulus artifact cancellation apparatus. These efforts were contributed out of his "own" time and are sincerely appreciated.

3. Charles Brice, Graduate Research Assistant.

Mr. Brice's contributions were in the areas of micro-electrode fabrication, preliminary animal surgery, and assistance with data collection. He also was responsible for general laboratory maintenance.

4. P. E. Cantrell, Graduate Student.

Mr. Cantrell assisted with animal surgery. He is another individual who provided a great amount of "free" labor. He is now pursuing a Ph. D. in a related area.

5. Norris Going, Graduate Research Assistant.

Mr. Going assumed all of Mr. Brice's duties except surgery and micro-electrode fabrication during the last three months of experimentation (January - March, 1974).

PAPERS ACCEPTED OR IN PREPARATION

1. "Artifact Reduction Techniques For Use in Recording Primary Auditory Nerve Fiber Responses to Sinusoidal Electrical Stimulation," to be submitted to the Journal of the Acoustical Society of America.
2. "Cochlear Responses to Externally Applied Electric Currents," accepted for presentation at the 27th Annual Conference on Engineering in Medicine and Biology, Philadelphia, October 6-10, 1974.

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APPENDIX

Characteristics of the Stimulating Electrodes

A most interesting and possibly significant aspect of this project concerned the observations we were able to make on electrical properties of the stimulating electrodes. These comments should prove useful to those who wish to initiate further research into cochlear electro-stimulation using acute animal preparations. (These electrodes would not be suitable for long-term use.)

The need for electrode information came about when we first attempted to use the artifact suppression technique described in the text. Recall that the method involves cancellation (with a differential amplifier) of an "artifact only" signal with an "artifact plus nerve response" signal. The "artifact only" signal was obtained with a phase-shifting technique involving linear filtering, which was not applied to the other signal. Therefore, any non-linear distortion of either or both of the two signals would render the method useless since the artifact would appear differently in the two channels. When the technique was initially tried, we discovered that cancellation was not effective and concluded that there were distortion-producing non-linearities operating within the stimulating and/or recording systems.

In an effort to locate the non-linearity, we first investigated the stimulating electrodes and found that they were the source of the distortion. At the time, we were using the 1.2 mm x 0.005" bare platinum wires implanted in the manner described by Walloch et al. (1973). They were tested by observing voltage and current waveforms obtained when currents

were passed between two 0.005" platinum wires located 2 mm apart and immersed 1.2 mm into 0.1 cc of Ringer's solution.

Results from such tests showed that with sinusoidal excitation producing current magnitudes large enough for cochlear stimulation, bare platinum electrodes exhibit voltage-current relationships which not only are non-linear, but also are time-varying. In fact, the data were so unrepeatable as to make any quantitative description impractical. In general, electrode voltage showed minimal distortion, but the current waveform was highly distorted, even with currents as small as $7.5 \mu\text{a}$ (peak-to-peak) (1.57 ma/cm^2) at 100 Hz. For several tests a rough measure of electrode impedance was obtained by dividing the peak-to-peak excitation voltage by the peak-to-peak current amplitude for increasing values of voltage. The non-repeatability and non-linearity of the results are indicated in Table A.1, which gives voltage, current, and impedance values for two runs (at 100 Hz) in which all experimental parameters were identical.

V_{pp} (volts)	I_{pp} (μa)	Z (K-ohms)
0.15	15	10
0.3	32.5	9.2
0.6	75	8.0
1.2	160	7.5
2.4	600	4.0
0.15	10	15
0.3	17.5	17
0.6	42.5	14
1.2	100	12
2.4	500	4.8

Table A.1. Voltage, current, and impedance measurements for platinum stimulating electrodes. V_{pp} , peak-to-peak electrode voltage; I_{pp} , peak-to-peak electrode current; Z , impedance of the electrode pair computed from V_{pp}/I_{pp} . See text for experimental details.

The same tests were run with 0.005" bare silver wires, and similar non-linear and time-varying characteristics were found.

At this point it became clear that a different electrode with significantly less non-linearity had to be found. Furthermore, we also wished to reduce the electrode impedance, which would in itself reduce the artifact because less voltage would be required to drive stimulating currents. To this end, the tests described above were conducted on 0.005" silver wires which had been chlorided according to the method given by Silver (1958). Fortunately, these electrodes exhibited very little distortion in the current waveform, and were much more stable and linear than the bare silver or platinum electrodes. The impedance of the pair was about 600 ohms at 100 Hz and remained essentially the same over a wide range of current amplitudes. Furthermore, the results were generally quite repeatable. As excitation frequency was increased, the impedance decreased, reaching about 260 ohms at 30 KHz.

The silver-silver chloride electrode system was adopted and used in the last four preparations (guinea pigs 341-344), two of which (341 and 344) yielded units responsive to the currents. In one of these animals, in vivo impedance measurements showed impedance levels about twice as great as those determined from in vitro tests, due probably to the small volume of conducting fluid available in the basal turn.